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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/537,564	08/28/2006	Peter Richardson	13425-170US1	4551

26161 7590 02/07/2008

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EXAMINER	
CRANE, LAWRENCE E	
ART UNIT	**PAPER NUMBER**
1623	

MAIL DATE	DELIVERY MODE
02/07/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/537,564	RICHARDSON, PETER	
	Examiner	Art Unit	
	L. E. Crane	1623	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *November 19, 2007 (amendment)*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *11-46* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *11-46* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *03 June 2005* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *08/03/2007*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Claims **1-10** were previously cancelled, claims **11-31** have been amended, the disclosure has been amended at numerous locations, the Abstract has been amended, and new claims **32-46** have been added as per the amendment filed November 19, 2007. One Information Disclosure Statement (1 IDS) filed August 3, 2007 has been received with copies of all cited non-US references and made of record.

Claims **11-31** remain in the case.

Note to applicant: when a rejection refers to a claim **X** at line y, the line number "y" is determined from the claim as previously submitted by applicant in the most recent response including ~~lines deleted by line through~~.

Claims **32-46** are rejected under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The instant disclosure fails to provide adequate written description of the "prevention" of pain (see claims **32** and claims dependent therefrom) associated with any disease condition by the administration of the single compound (2-methoxyadenosine) listed herein as an active ingredient. In addition, there is no written description supporting adequately the co-administration of 2-methoxyadenosine with any other substance known to act as an analgesic. And the instant disclosure fails to provide any description of the effective treatment of pain associated with any cancer including pancreatic cancer or brain cancer, any auto-immune disease, epilepsy, neurodegeneration including Alzheimer's Disease, HIV, AIDS, ARC, silicosis, myasthenia gravis, Crohn's Disease, bacterial meningitis, and nearly all of the other diseases listed generically or specifically in any of claims **32-46**.

Applicant's arguments with respect to claims **11-31** have been considered but are moot in view of the new grounds of rejection. This new ground of rejection was necessitated by applicant's amendments.

Examiner notes applicant separation of the "prevention" limitation by adding a separate set of claims, in particular claims **32-46**. However, the term "prevention" implies a heightened

standard of enablement, heightened to a level similar to that applied in the vaccine art. Examiner has inspected the Figures and the explanations thereof, but does not see any examples wherein applicant has actually demonstrated that pain has been prevented, as opposed to pain being treated, a possibility clearly addressed by, and enabled by, the supplied examples. Because applicant has supplied some experimental data, PTO policy permits supplementation thereof by filing a declaration under 37 C.F.R. §1.132 is a possible mechanism to provide the necessary additional experimental data, if available, to separately enable the newly added claims. Or, if the enabling data is already present, examiner, and the record, would benefit from a more clearly presented, and/or more detailed, description thereof. The Figures in particular are not easy to decipher in view of their small size, their unclear or incomplete definition of graphical symbols, and the consequential difficulty in establishing a clear understanding of what the various graphical representations actually mean.

Claims **32-46** are rejected under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The instant disclosure fails to provide adequate written description of the "prevention" of pain associated with any disease condition by the administration of the single compound (2-methoxyadenosine) listed herein as an active ingredient. In addition, there is no written description supporting adequately the co-administration of 2-methoxyadenosine with any other substance known to act as an analgesic. And the instant disclosure fails to provide any description of the effective treatment of pain associated with any cancer including pancreatic cancer or brain cancer, any auto-immune disease, epilepsy, neurodegeneration including Alzheimer's Disease, HIV, AIDS, ARC, silicosis, myasthenia gravis, Crohn's Disease, bacterial meningitis, and nearly all of the other diseases listed generically or specifically in any of claims **11, 15 and 18**.

Claims **11-31** are rejected under 35 U.S.C. §112, first paragraph, because the specification, while being enabled for the treatment of inflammation and hypertension, does not reasonably provide enablement for the treatment of any other disease condition. The

specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The fundamental issue here is whether practicing the full scope of the instant invention is possible without undue experimentation. As provided for in *In re Wands* (858 F.2d 731, 737; 8 USPQ 2d 1400, 1404 (Fed Cir. 1988) the minimum factors to be considered in determination of whether a conclusion of "undue experimentation" is appropriate are as follows:

A. The breadth of the claims: The instant claims are directed to the treatment of pain associated with a vast array of specifically named, and generically defined, disease conditions wherein the instant disclosure fails to define how to effective treat the vast majority thereof. The claims are therefore deemed to be excessively broad in scope.

B. The nature of the invention: The invention defined by the listed claims is directed to the treatment of a vast array of diseases by the administration of a 2-methoxyadenosine to a host in need of treatment.

C. The state of the prior art: The prior art identifies the claimed active ingredients but does not identify the instant claimed pharmacological activity.

D. The level of one of ordinary skill: One of ordinary skill would be expected to be familiar with the details of the medicinal treatment of the diseases listed in claims dependent from claim **32**, a literal impossibility because no one practitioner, or even a dozen practitioners combined, would be able to meet this requirement.

E. The level of predictability in the art: In view of the absence of teachings herein and in the prior art to provide relevant guidance directed to treatment of each of the vast array of disease conditions listed in claims dependent from claim **32**, the predictability of the art is deemed to be very low.

F. The amount of direction provided by the applicant: The instant disclosure, as noted above, only supplies two and one-half pages of guidance and an indication of how to treat pain associated with only a few model test hosts wherein the pain has been induced artificially.

G. The existence of working examples: The existence and the content of examples is described in the previous paragraph.

H. The quantity of experimentation needed to make or use the invention based on the content of the disclosure is deemed to be excessive because the bare minimum of examples in the instant disclosure at pages 7-9 is entirely inadequate to provide the guidance necessary to practice the instant claimed methods in the treatment of pain predictably in the vast majority of the disease conditions listed in claims dependent from claim **32**.

Applicant's arguments with respect to claims **11-31** have been considered but are moot in view of the new grounds of rejection. This new ground of rejection was necessitated by applicant's amendments.

Applicant is referred to the comments following the previous rejection wherein the issue of enablement is specifically addressed. .

Claims **14, 18, 27 and 44** are rejected under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In claim **14** the term "disease that causes damage to sensory neurons" renders the claim incomplete because the particular diseases implied by said term have not been defined in the claim.

Applicant's arguments filed November 19, 2007 have been fully considered but they are not persuasive.

Applicant argues that one or ordinary skill would known the plain meaning of the instant cited term. Examiner respectfully disagrees. The noted term is both generic and functional, and therefore encompasses subject matter known in the art and presently unknown subject matter, i.e. diseases not yet identified and therefore not yet known in the art. In view of the requirement of the noted statute for well defined metes and bounds in patent claims, the above rejection has been repeated. Applicant is respectfully requested to amend accordingly.

In claim **18** at line 4, the term "arthritic conditions" has not been further defined in the claim, thereby rendering the claim incomplete.

Applicant's arguments filed November 19, 2007 have been fully considered but they are not persuasive.

Applicant argues that one or ordinary skill would known the plain meaning of the instant cited term. Examiner respectfully disagrees. The noted term is both generic and functional, and therefore encompasses subject matter known in the art and presently unknown subject matter, i.e. diseases not yet identified and therefore not yet known in the art. In view of the requirement of the noted statute for well defined metes and bounds in patent claims, the above rejection has been repeated. Applicant is respectfully requested to amend accordingly.

In claim **27** at line1 the term -- further comprising -- or the like is missing as providing a proper basis for expansion of the scope of the subject matter of claim **11**. For this reason claim **27** lacks proper antecedent basis in claim **11**. See also claim **44** wherein the same problem reoccurs. In addition in both claims **27 and 44**, examiner suggests that clarity would be improved by amendment of the term "an analgesic agent" to read -- a second analgesic agent -- , because the compound spongosine is in effect -- the first analgesic agent --. Alternatively, applicant may elect to cancel claims **27** and claims dependent therefrom, and likewise claim **44** and claims dependent therefrom because the term "comprises" in claim **11** already includes coverage of all method of treatment subject matter that includes the subject matter of claims **11 and 32**, respectively.

Applicant's arguments filed November 19, 2007 have been fully considered but they are not persuasive.

Applicant has argued that the amendment of the noted claim is sufficient and that no further amendment is required. Examiner respectfully disagrees. The amended claim asserts the method of treatment of claim **11** wherein " ... an analgesic agent is co-administered to the subject," subject matter that is <u>not</u> found in claim **11**. Because applicant is claiming a "method of treating" and has styled claim **11** with the term "comprises," a judicially recognized term of art in patent claim construction meaning -- includes --, applicant is free to add subject matter, but the price for exercise of this right is to give notice of the expansion of claim scope to the

party reading dependent claim **27**, notice given by insertion of the suggested term -- further comprising -- therein. Applicant is encouraged to amend accordingly in both claim **27** and in newly added claim **44**.

The non-statutory double patenting rejection, whether of the obviousness-type or non-obviousness-type, is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent. *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969); *In re Vogel,* 422 F.2d 438, 164 USPQ 619 (CCPA 1970); *In re Van Ornam,* 686 F. 2d 937, 214 USPQ 761 (CCPA 1982); *In re Longi,* 759 F.2d 887, 225 USPQ 645 (Fed. Cir 1985); and *In re Goodman,* 29 USPQ 2d 2010 (Fed. Cir. 1993).

A timely filed terminal disclaimer in compliance with 37 C.F.R. § 1.321(b) and (c) may be used to overcome an actual or provisional rejection based on a non-statutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 C.F.R. §1.78(d).

Effective January 1, 1994, a registered attorney or agent or record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 C.F.R. §3.73(b).

Claims **11-46** are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims ***16-33*** of copending Application No. **10/547,455**. Although the conflicting claims are not identical, they are not patentably distinct from each other because the methods of treatment both appear to include or imply the treatment of pain and the alleged active ingredients (2-alkoxyadenosines and their 3'-deoxy analogues) are directed to substantially overlapping subject matter.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Applicant's arguments filed November 19, 2007 have been fully considered but they are not persuasive.

Applicant argues that the above ground of rejection is the only remaining rejection not overcome by applicant's arguments, and therefore that examiner is requested to withdraw same because the noted copending application has not been allowed. Examiner refers applicant to the remainder of the instant Office action for several repeated rejections, rejections that make allowance at this time problematic. Therefore, in view of two related cases wherein overlapping subject matter has been claimed, the above and the immediately following rejections haven been repeated in part because it is unclear whether any case will be allowed, let alone allowed first allowed, at this time.

Claims **11-46** are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims ***13-24*** of copending Application No. **10/547,454**. Although the conflicting claims are not identical, they are not patentably distinct from each other because the methods of treatment both appear to include or imply the treatment of pain and the alleged active ingredients (2-alkoxyadenosines and their 3'-deoxy analogues) are directed to substantially overlapping subject matter.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Applicant's arguments filed November 19, 2007 have been fully considered but they are not persuasive.

Applicant is referred to the remarks following the immediately preceding rejection.

Claims **11-46** of this application conflict with ***13-24*** of copending Application No. **10/547,454** and ***16-33*** of copending Application No. **10/547,455**. 37 C.F.R. §1.78(b) provides that when two or more applications filed by the same applicant contain conflicting claims, elimination of such claims from all but one application may be required in the absence of good and sufficient reason for their retention during pendency in more than one application. Applicant is required to either cancel the conflicting claims from all but one application or maintain a clear line of demarcation between the applications. See MPEP §822.

The following is a quotation of 35 U.S.C. §103(**a**) which forms the basis for all obviousness rejections set forth in this Office action:

"A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made."

Claims **11-46** are rejected under 35 U.S.C. §103(**a**) as being unpatentable over **Fukunaga '290** (PTO-892 ref. **C**) in view of **Fukunaga et al. '650** (PTO-892 ref. **A**) and further in view of **Ueeda et al.** (PTO-892 ref. **R**).

The instant claims are directed to methods of treatment wherein 2-methoxyadenosine is administered to treat pain associated with a disease condition selected from a vast array of possibilities.

Fukunaga '290 at column 4, lines 23-54 discloses that carefully controlled continuous administration of adenosine or analogues thereof can cause relief from pain and inhibition of "stress" wherein the symptoms of "stress" are also commonly associated with inflammation. The **'290** reference also teaches that adenosine or its analogues can be administered at rates that avoid hypotension while producing the desired degree of pain relief.

The **Fukunaga '290** reference does not expressly disclose 2-methoxyadenosines as an active ingredient in any method of treatment.

Fukunaga et al. '650 discloses at column 18, lines 48-61 that adenosine administered with sufficient amount of catecholamine modulates the undesirable side effects associated with administration of the anesthetic fentanyl. In addition at column 23, lines 30-47 this reference discloses in general that large dosages of adenosine in combination with a catecholamine are effective in minimizing the damage from a number of disease conditions including ischemia. Subsequent examples at columns 23-24 teach that adenosine may be substituted by a number of different adenosine analogues with similar outcomes. The antihypertensive, antinociceptive (pain inhibiting), and the anti-inflammatory effects of adenosine are notoriously well known in the art as disclosed in the **'650** reference at columns 1-4.

Fukunaga et al. '650 does not expressly disclose 2-methoxyadenosine as an active ingredient in any method of treatment.

Ueeda et al. discloses at page 1353 that the compound 2-ethoxyadenosine has binding constants at adenosine receptors that vary very little from the binding constants for adenosine, for R-PIA and for NECA, a teaching supporting the conclusion that substitution of an adenosine analog for adenosine would be expected to produce a similar effect, including the analgesic effect on pain.

It would have been obvious to a person of ordinary skill in the art at the time the invention was made to substitute compounds very closely analogous to the compounds disclosed by **Ueeda et al.** into the methods disclosed by the **Fukunaga** references because the **Fukunaga** references explicitly teach the pharmacological equivalence of adenosine and adenosine analogues.

One having ordinary skill in the art would have been motivated to combine these references because all three references are directed to overlapping disclosures of the medicinal administration of adenosine and analogues of adenosine, including one compound defined herein as an active ingredient, to treat various disease conditions including pain, inflammation and hypertension.

Therefore, the instant claimed methods of administration of 2-methoxyadenosine to treat a variety of disease conditions including pain, inflammation and hypertension would have been obvious to one of ordinary skill in the art having the above cited references before him at the time the invention was made.

Applicant's arguments filed November 19, 2007 have been fully considered but they are not persuasive.

Applicant is respectfully requested to note that a precedent applies in the instant case. The Hass/Henze Doctrine (aka The Homology Rule) states that a methylene homologue of a known compound is prima facie unpatentable in the absence of a showing of unexpected results. The homology between compounds disclosed in the prior art and compounds included within the scope of the noted claims has been established. Therefore, In light of the Hass/Henze doctrine the instant claims are deemed to have been rendered obvious by the disclosure of the noted **Ueeda et al.** reference in view of the disclosures of the **Fukunaga** references. See *In re Hass et al.* (CCPA 1944) 141 F2d 122, 127, 60 USPQ 544, 548 and *In re*

Henze (CCPA 1950) 181 F2d 196, 85 USPQ 261. See also MPEP §2144.09 for more current commentary on this issue.

Specifically, the instant claimed active ingredient, 2-methoxyadenosine (aka spongosine), is a methylene homologue of the compound disclosed in **Ueeda et al.** (2-ethoxyadenosine).

Applicant's arguments may be summarized as noting the limitations of the **Ueeda et al.** reference, but not really overcoming examiner assertion that the compounds listed in **Ueeda et al.**, including adenosine, have binding constants (where measurement was possible) that vary very little. The point of examiner's rejection was to note that a compound exists and is known in the prior art (2-ethoxyadenosine disclosed by **Ueeda et al.**) that would been expected, based on the disclosures of the **Fukunaga** patents and **Ueeda et al.** to have pharmacological properties very similar to the compound (spongosine, aka 2-methoxyadenosine) applicant's claims and disclosure identify as an active analgesic. Applicant is respectfully requested to demonstrate with data, argumentation, other literature evidence, or some combination thereof, that the disclosure that spongosine's analgesic activity would have been unexpected in view of what is already known in the art about a homologous compound and other closely related "adenosine receptor agonists" and the finding that adenosine is itself a potent analgesic by the **Fukunaga** patents, as disclosed by the cited prior art. Examiner notes applicant comments criticizing the **Fukunaga** references concerning their observation that adenosine administration can induce serious side effects, and also that presumable the same serious side effects are specifically acknowledged by applicant in the claims directed to dosages. Therefore, the issue of side effects is not found by examiner to be dispositive in the current situation.

A side-by-side comparison of the analgesic effects of molar-equivalent dosages of adenosine (alone) and spongosine (alone) in the same animal model system would seem to be in order as a starting point for this determination. A sworn showing that the analgesic effect of spongosine is measurably, and unexpectedly, different from that of adenosine is essential: a statistical margin of error determination is important as is comparison with the range of variation in analgesic activity as a function of the relevant adenosine receptor binding constant(s) when compared with the other "adenosine compounds" listed in both **Ueeda et al.** and the **Fukunaga** references. In the absence of a this kind of sworn showing, examiner maintains that the rejection of record remains valid.

Applicant's amendment necessitated the new grounds of rejection. Accordingly, **THIS ACTION IS MADE FINAL**. Applicant is reminded of the extension of time policy as set forth in 37 C.F.R. §1.136(a).

A shortened statutory period for response to this final action is set to expire THREE MONTHS from the date of this action. In the event a first response is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 C.F.R. §1.136(a) will be calculated from the mailing date of the advisory action. In no event will the statutory period for response expire later than SIX MONTHS from the date of this final action.

Papers related to this application may be submitted to Group 1600 via facsimile transmission (FAX). The transmission of such papers must conform with the notice published in the Official Gazette (1096 OG 30, November 15, 1989). The telephone number to FAX (unofficially) directly to Examiner's computer is 571-273-0651. The telephone number for sending an Official FAX to the PTO is 571-273-8300.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Examiner L. E. Crane whose telephone number is **571-272-0651**. The examiner can normally be reached between 9:30 AM and 5:00 PM, Monday through Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ms. S. Anna Jiang, can be reached at **571-272-0627**.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group 1600 receptionist whose telephone number is **571-272-1600**.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status Information for unpublished applications is available through Private PAIR only. For more information about

the PAIR system, see < http://pair-direct.uspto.gov >. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at **866-217-9197** (toll-free).

LECrane:lec
01/31/2008

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